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WITNESS my hand this
Twenty-second day of October 2003

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AUSTRALIA

*Patents Act 1990*

# PROVISIONAL SPECIFICATION

Invention Title: **"AN IMPEDENCE CARDIOGRAPHY DEVICE"**

The invention is described in the following statement:

# HIGH RESOLUTION BIO-IMPEDANCE DEVICE

## TECHNICAL FIELD

The present invention relates to a device for measuring a biological parameter such as extracellular fluid in a person and in particular to a bio-impedance device for non-invasively measuring the cardiac output using impedance measurements at multiple frequencies.

## BACKGROUND OF THE INVENTION

Heart rate is typically determined by an electrocardiogram (ECG or EKG) and monitoring of the heart can provide useful information on the mechanical behaviour of the heart. The cardiac output (CO), which is a quantitative measure of blood flow, is one of the most useful parameters in assessing cardiac capability. However, it cannot be measured using standard ECG, which does not reflect the real pumping action of the heart.

Invasive and non-invasive techniques are available for measurement of cardiac output. The invasive techniques are considered most accurate, however, the risks associated with this technique are unacceptable since they require direct access to the arterial circulation.

Impedance cardiography is a non-invasive method which has the potential for monitoring the mechanical activity of the heart with minimised risk to the patient. One such system is known from United States Patent No. 5 309 917 which describes a system and method of cardiac monitoring in which thoracic impedance and EKG signals are gathered and processed. Inner and outer pairs of electrodes are applied to a patient such that a

fluctuating alternating current is applied to the patient through the outer electrodes. The inner pair of electrodes are provided to sense voltage levels on the patient from which thoracic impedance is determined.

A preprocessor excites the electrodes at a high frequency (100 kHz) and low amplitude (up to 4mA RMS) alternating current. The preprocessor outputs four analog signals: the mean thoracic impedance signal (Z0), the change in thoracic impedance signal (delta Z or $\Delta Z$), the time-derivative impedance signal (dZ/dt) and the electrocardiogram signal (ECG). The time-derivative impedance signal is converted to the frequency domain to determine cardiac events, stroke volume and cardiac output.

A major drawback of the above method and system is a single frequency is used to measure impedance at the electrodes. The use of a single frequency presents inaccuracies in determining cardiac activity and output.

Another prior system is described in United States Patent No. 6 339 722. Unlike the system above, the patent describes an apparatus for measuring a biological parameter such as cardiac output using a current source generating two signals of different frequencies. The current source, which supplies the measuring alternating measuring current, has an electrically symmetrical configuration. The current source is provided with a galvanic separation in relation to the measuring part of the instrument. A measuring current is provided with constant amplitude on at least two frequencies, a low frequency and a high frequency, in a frequency range of upto 2000 kHz. A first low frequency and first high frequency are coupled to

a first two pairs of electrodes for local bio-impedance measurement in a segment of a patient's body, removed from the heart.

A common drawback of the above systems is the use of current sources to generate the measuring alternating current at the electrodes. Current signals are prone to artefacts from the current source generator in the high frequency end.

Yet another drawback of the above system is the bio-impedance measurement includes a combined measure of intracellular and extracellular fluids thereby diminishing the accuracy of the measurement for cardiac output.

## OBJECT OF THE INVENTION

It is an object of the invention to provide an improved bio-impedance device for measuring cardiac output.

It is a further object of the invention to provide a bio-impedance device for measuring extracellular fluids (blood volume) only in a person.

## SUMMARY OF THE INVENTION

In one form, although it need not be the only or indeed the broadest form, the invention resides in a method of determining the volume of extracellular fluid in a person comprising the steps of:

attaching at least two pairs of electrodes to a person;

generating a measuring current having a known variable voltage by a power source electrically isolated from said person;

applying said current to a first pair of said at least two pairs of electrodes continuously at multiple frequencies;

converting a voltage measured at a second pair of electrodes into bio-impedance signals, for each frequency of said current;

processing and converting said bio-impedance signals into a frequency domain; and

extrapolating from said bio-impedance signals an impedance value at zero frequency ($R_0$), at a plurality of time intervals for each frequency, to determine the volume of extracellular fluid in said person.

In a preferred form the step of extrapolating comprises the further steps of:

sampling the bio-impedance signals to obtain a sampled bio-impedance;

applying a time to frequency domain transform, to said sampled signal to obtain transformed bio-impedance signals;

filtering the transformed bio-impedance signals and isolating each frequency to determine the impedance for each frequency at each time interval; and

extrapolating an impedance value at zero frequency from the filtered bio-impedance signals at each frequency;

The change in the impedance value over time and the rate of change in the measured bio-impedance signal dZ/dt is preferably used to determine impedance parameters to calculate a cardiac output of said person.

In another form of the invention there is provided an apparatus for

non-invasively measuring extracellular fluid in a person, said apparatus comprising:

at least two pairs of electrodes adapted to be attached to a person;

a power source, electrically isolated from said person, generating a current at a known variable voltage, which is applied to a first pair of said at least two pairs of electrodes continuously at multiple frequencies;

converter means for converting a voltage measured at a second pair of electrodes into bio-impedance signals, for each frequency of said current;

signal processing means for converting said bio-impedance signals into a frequency domain; and

means for determining the volume of extracellular fluid in said person by extrapolating from said bio-impedance signals for each frequency, at a plurality of time intervals, an impedance value at a zero frequency ($R_0$).

Preferably, the change of volume of the extracellular fluid, over time, is indicative of cardiac output in said person. The volume of the extracellular fluid may indicate a stroke volume (SV) of the person's heart.

Preferably a time derivative of said bio-impedance signal is mathematically obtained using the extrapolated impedance at zero frequency ($R_0$).

Preferably, the multiple frequencies at which the current is applied is in the range of 2 kHz to 2000 kHz.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG 1 is a circuit diagram of an electric circuit formed with a biological

tissue;

FIG 2 is an illustrative embodiment of a high resolution bio-impedance device in accordance with the invention;

FIG 3 is a Cole-Cole plot of bio-impedance signal data over a range of frequencies; and

FIG 4 is a flow chart showing the process steps for obtaining bioimpedance signals and measuring extracellular fluid in accordance with an embodiment of the invention.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In a preferred form, the invention will be described with reference to a bio-impedance device for measuring a cardiac output such as stroke volume of the heart in a person. However, it should be noted that the invention could also be realised to measure other biological parameters relating to bodily fluids such as stroke volume, thoracic fluid content, ejection fraction, pulmonary wedge pressure, ejection interval and cardiac index.

There are several lightly invasive methods available for assessing the heart, many of which involve the use of venous or arterial catheters into (or in very close proximity to) the cardiac chambers (*eg* thermo- or dye-dilution).

Non-invasive procedures are limited to echocardiography and impedance cardiography. Echocardiography cannot be performed on a continuous basis and requires expert operator skills. The technique of impedance cardiography is completely non-invasive. It can be used for continuous monitoring, does not require expert operator skills and can be

performed on virtually all subject groups including critically ill, elderly or pregnant individuals. However, while the technique of impedance cardiography has many advantages its correlation and agreement with other techniques has been reported as less than ideal and it generally overestimates the cardiac output particularly in clinical subjects as discussed by: Spiering et al, "Comparison of impedance cardiography and dye dilution method for measuring output", Heart, 1998; 79(5): 437, 441.

The theory behind bioelectrical impedance can be explained in relation to a conducting cylinder. The impedance of a conducting cylinder is related to the conductor length, cross sectional area, and signal frequency. Using a constant signal frequency the impedance is given by:

$$Z = \frac{\rho L}{A}$$

where Z = impedance ($\Omega$)

$\rho$ = resistivity of the medium ($\Omega$)

L = conductor length (cm)

and A = cross sectional area ($cm^2$)

Using V = volume ($cm^3$) = A x L and eliminating A

Yields: $V = \frac{\rho L^2}{Z}$ **equation 1**

Referring now to FIG 1, there is shown a simple equivalent circuit representing biological tissue. The extracellular current pathway is purely resistive, while the intracellular current pathway has an associated capacitance due to the cell membrane. The relative magnitudes of the extracellular and intracellular components of an alternating current (AC) are

frequency dependent. At zero frequency the capacitor acts as an insulator and all of the current passes through the extracellular fluid. Hence the measured impedance, $Z_0$, at zero frequency is the impedance of the extracellular fluid. At higher frequencies the capacitor has a finite impedance and the current passes through both branches of the parallel circuit model. The measured impedance at these non-zero frequencies is therefore due to both the extracellular and intracellular fluid volumes.

The volume in equation 1 is the volume of the conducting medium. If there are changes in the volume of the conducting medium with time, as is the case of continuously varying blood volumes in the region of the heart, then the change in conducting volume is related to the change in impedance by the following equation discussed by Geddes et al in "Principles of applied biomedical instrumentation": John Wiley & Sons, 1989, New York:

$$\Delta V = -\langle \frac{\rho L^2}{Z_B^2} \rangle \Delta Z \qquad \textbf{equation 2}$$

$\Delta V$ = blood volume change

$\rho$ = resistivity of blood

L = distance between measurement electrodes

$Z_B$ = baseline impedance value

$\Delta Z$ = change in impedance (attributable to stroke volume)

The frequency commonly used in impedance cardiography systems is generally selected between 70 and 100 kHz.

An important parameter of a heart function is the stroke volume (SV) of the heart. Stroke volume can be determined by manipulating equation 1

as was developed by Kubicek et al in: "Development and evaluation of an impedance cardiac output system", Aerospace Medicine, 1966; 37:1208, 1212. The stroke volume is represented as:

$$SV = \frac{\rho L^2 \langle dZ/dt \rangle_{max} VET}{Z_B^2} \qquad \textbf{equation 3}$$

where: SV = stroke volume

$(dz/dt)_{max}$ = maximum rate of change in measured impedance at the beginning of systolic cycle.

VET = left ventricular ejection time.

However, this technique requires the accurate measurement of the inter-electrode distance placed on a person and also the measurement of haematocrit to determine blood resistivity. A modification to this algorithm was introduced by Bernstein DP: "A new stroke volume equation for thoracic electrical bio impedance: theory and rationale", Critical Care Medicine, 1986; 14:904,909. This relationship is currently used by the majority of impedance cardiography instruments.

$$SV = \frac{L'^3 \langle dZ/dt \rangle_{max} VET}{Z_B} \qquad \textbf{equation 4}$$

where: L'= thoracic length estimated from the subject's height and weight using a nomogram, L' also accounts for blood resistivity.

The overall impedance of the thorax varies between subjects. The quoted range is 20 to 48 Ω at frequencies between 50 kHz and 100 kHz. Critchley", L. A. H. in "Impedance cardiography, the impact of a new technology", 1998, Anaesthesia 53: 677-684, quotes the variation in transthoracic impedance due to the cardiac cycle as approximately 1% of the

overall impedance of the thorax. This leads to a very 'fragile' signal with a very low signal to noise ratio.

Precise identification of the impedance signal, is essential if accurate measurements of both $dZ/dt_{max}$ and ventricular ejection time are to be made. As noted above, signal to noise ratio in present systems is very low which leads to inaccuracies when these parameters are measured. The problem is exacerbated when the patient moves or exercises.

The most important significant aspect of the accuracy of transthoracic electrical bio impedance measurements resides in the signal processing of the measured bio impedance signal.

Referring now to FIG 2, there is generally shown a high resolution bio-impedance device 1 in accordance with invention. An isolated current source 2 supplies an alternating current of up to 4mA to a pair of source electrodes 3 attached to the thoracic region of a person 4. A signal generator 5 supplies multiple frequencies to the current source 2 for application to the source electrodes 3. The frequency range is between 2 kHz and 2000 kHz.

A voltage is produced at a pair of potential electrodes 6 due to the current applied at source electrodes 3. A data acquisition module 7 converts the measured voltage at the potential electrodes 6 and the measuring current for each frequency, into bio-impedance signals indicative of the bio-impedance of the thoracic region of person 4.

The current source 2 is electrically isolated from the mains power and the person 4. The specifications of the power source conforms to Australian

standards which permit, a maximum of 32V and a maximum current of 100μA at 10 kHz. This current limit increases to an upper threshold of 1mA at 1000 kHz.

Source electrodes 3 comprise circuitry for efficiently applying the current at various frequencies to a person 4. Transformers and amplifiers are provided to accurately deliver the voltage and measure the applied current. Similarly, potential electrodes 6 also comprise a high input impedance amplifier and driven shields, transformer and filtering to eliminate interference and provide gain to the potential difference.

To facilitate attachment of the electrodes, clips are provided with shielding from stray current to isolate from the person 4. The cables have bandwidth sufficient to carry the range of frequencies at low current levels and haven driven shields to minimize capacitive leakage.

The data acquisition module 7 receives the measured voltage from the potential electrodes 6 and a measured current from the current source 2 to measure the bio-impedance in the thoracic region. The bio-impedance signals are converted to the frequency domain using Fast Fourier Transform (FFT).

The data acquisition module 7 is comprised of a 14 bit, 4 channel, 2.5 MS/s per channel A/D converter.

Electrodes of an ECG 8 are attached to the thoracic region of person 4 to obtain cardiographic signals of heart activity. The ECG is used to determine the electrical timing of the cardiac cycle to augment the information provided by the bioimpedance signal.

A processing unit 9 such as a computer with processing software receives the ECG data and FFT of the bio-impedance signals and performs a data analysis function 10.

Referring now to FIG 4, there is shown the steps of obtaining bioimpedance signals and measuring extracellular fluid and other cardiac parameters in accordance with an embodiment of the invention.

The current source 2 collects a signal representative of the applied measuring current and the measured voltage from the potential electrodes 6 at steps 11 and 12. A data acquisition module 7 converts the measured voltage and the measuring current for each frequency into a frequency domain at 13.

An algorithm incorporating calibration coefficients is executed at 14 to calibrate the measured impedances. A calibration card of circuits of known impedances can be provided which is used to calibrate the source and potential electrodes of the device.

The processing unit 9 performs FFT analysis on short time blocks of sampled bio-impedance data at 15. The transformed data is digitally filtered (not shown) and individual frequencies are isolated to determine the impedance for each frequency, for each time block. An impedance value at zero frequency $R_0$ is extrapolated from the impedance values at each frequency.

A Cole-Cole plot as shown in FIG 3, is generated at 16 where, the bio-impedance data over the range of frequencies is made to fit the known theoretical circular locus and $R_0$ is extrapolated at 17. $R_0$ is the theoretical

impedance to a DC signal as shown in FIG 3 and corresponds to the impedance of extracellular fluid or water (ECW). The ECW impedance values can be plotted with respect to time and correlated to the ECG signal.

Process steps 11 to 17 are repeated for each time block between 1 ms to 20 ms.

The processing unit further processes the change of impedance Z over time and the rate of change in the measured impedance at the systolic cycle of the heart, dZ/dt at 18 and 19 to determine impedance parameters $Z_0$ (baseline impedance), $dZ/dt_{max}$ and LVET.

The cardiac output is obtained by calculating either equation 3 or 4 using the parameters obtained above. The equations, when solved provide the stroke volume of the heart. However, the above parameters are further processed at 20 to determine other cardiac output such as ejection fraction or other values indicative of heart activity.

The data acquisition module 7 can be fully integrated with digital signal processors to conduct FFT on digitised block of bio-impedance data, digital filtering and generation of Z versus time and dZ/dt versus time waveforms. In this arrangement a separate processing unit 9 may not be required to perform data analysis of the bio-impedance signals.

The present invention provides an improved bio-impedance device which measures cardiac output using multiple frequencies to determine bio impedances at each frequency, at each time block and to calculate the extracellular fluid volume $R_0$ (blood volume) in each time block.

The invention has been described with reference to an exemplary

embodiment. However, it should be noted that other embodiments are envisaged within the scope and spirit of the invention.

Dated this Ninth day of October 2002

QUEENSLAND UNIVERSITY OF TECHNOLOGY

By its Patent Attorneys

FISHER ADAMS KELLY

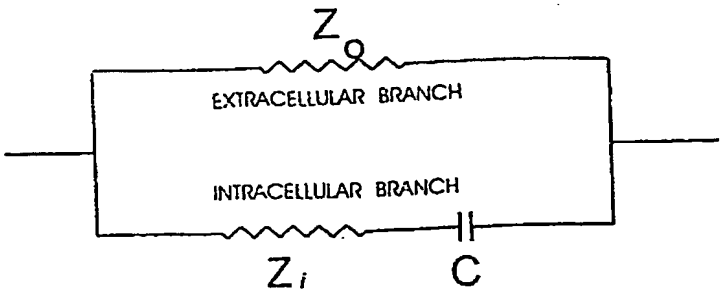
Z
EXTRACELLULAR BRANCH
INTRACELLULAR BRANCH
Zi
C

FIG 1

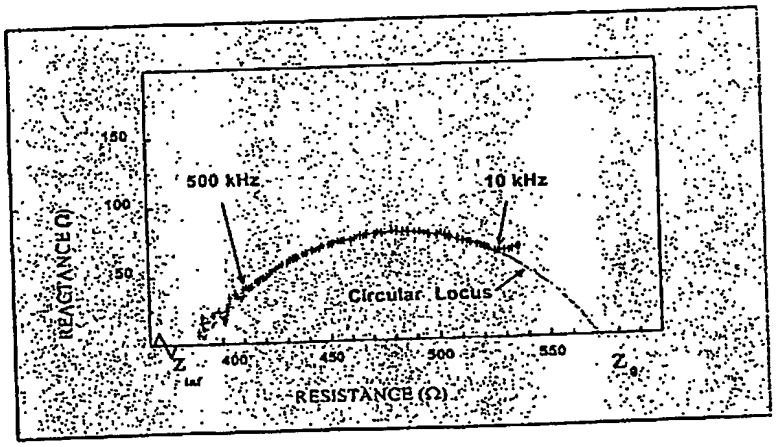
150
100
50
REACTANCE (Ω)
500 kHz
10 kHz
Circular Locus
400
450
500
550
RESISTANCE (Ω)

FIG. 3

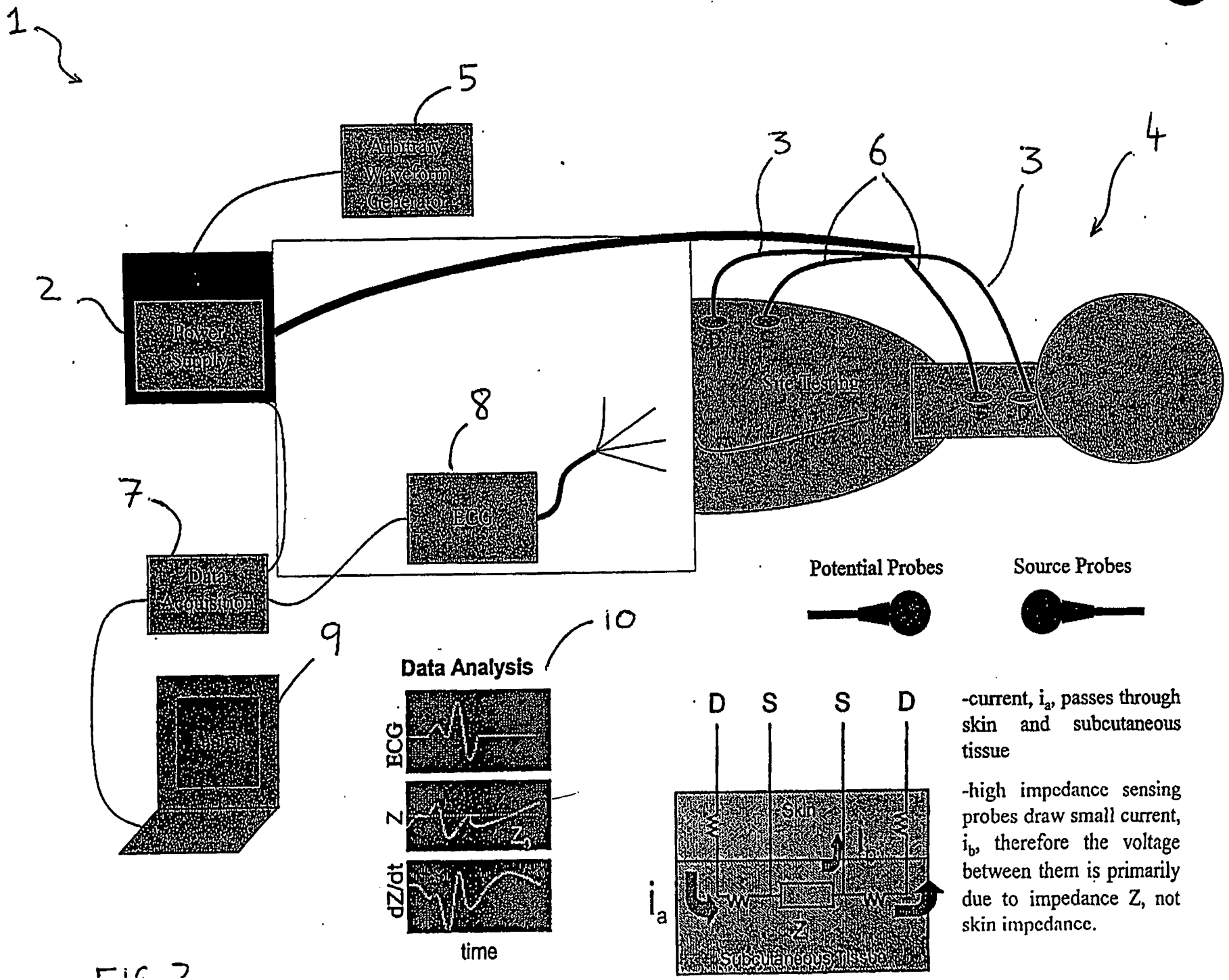
1
5
Arbitrary Waveform Generator
2
Power Supply
3
6
3
4
Site Testing
8
ECG
7
Data Acquisition
9
10
Data Analysis
ECG
Z
dZ/dt
time
Potential Probes
Source Probes
D
S
S
D
Skin
Subcutaneous Tissue
$i_a$
$i_b$
-current, $i_a$, passes through skin and subcutaneous tissue
-high impedance sensing probes draw small current, $i_b$, therefore the voltage between them is primarily due to impedance Z, not skin impedance.

FIG 2

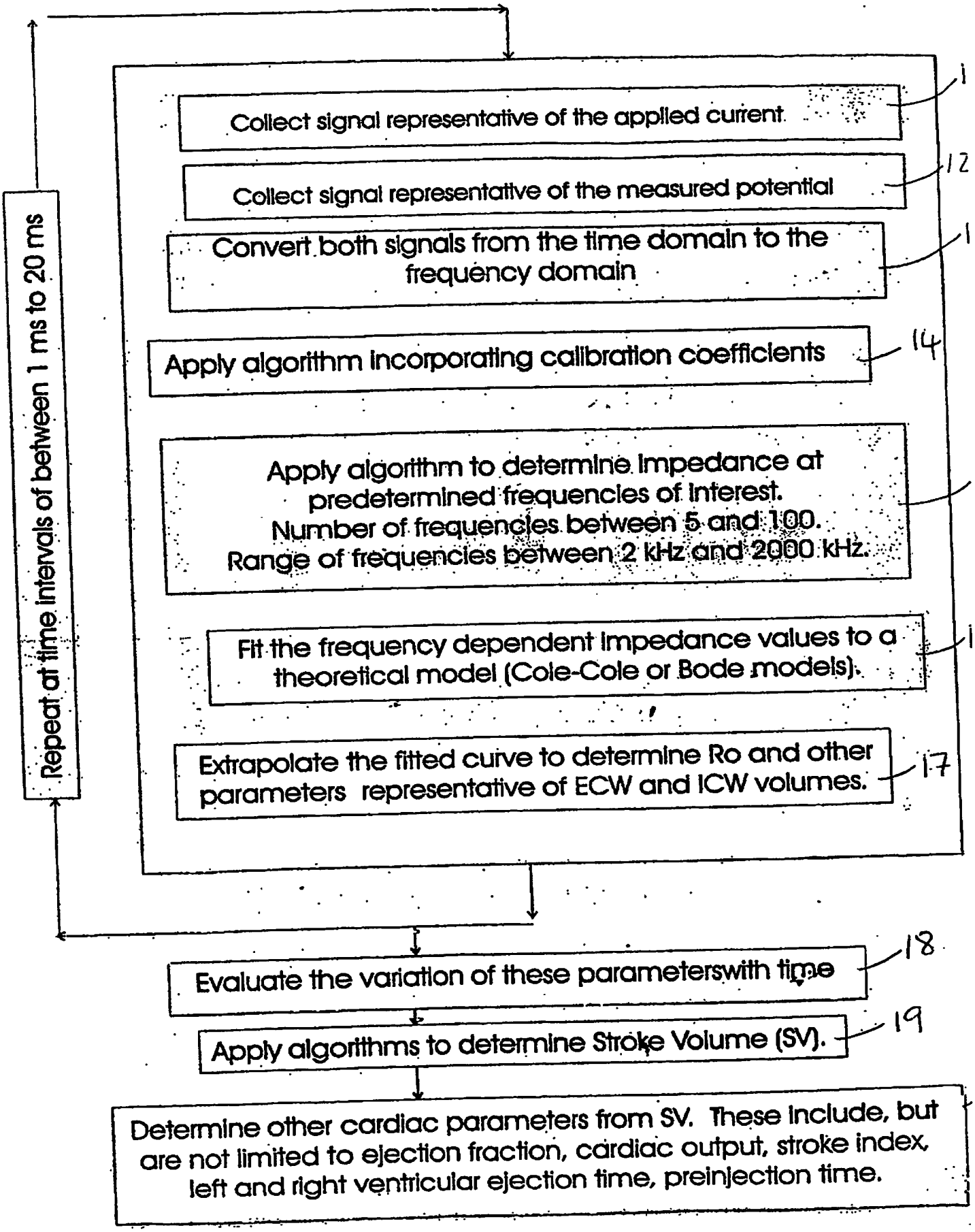
Repeat at time intervals of between 1 ms to 20 ms
Collect signal representative of the applied current
Collect signal representative of the measured potential
Convert both signals from the time domain to the frequency domain
Apply algorithm incorporating calibration coefficients
Apply algorithm to determine impedance at predetermined frequencies of interest.
Number of frequencies between 5 and 100.
Range of frequencies between 2 kHz and 2000 kHz.
Fit the frequency dependent impedance values to a theoretical model (Cole-Cole or Bode models).
Extrapolate the fitted curve to determine Ro and other parameters representative of ECW and ICW volumes.
Evaluate the variation of these parameterswith time
Apply algorithms to determine Stroke Volume (SV).
Determine other cardiac parameters from SV. These include, but are not limited to ejection fraction, cardiac output, stroke index, left and right ventricular ejection time, preinjection time.

FIG 4